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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/309,038	05/10/1999	PETER BERNARD HEIFETZ	A-30496B	7012

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EXAMINER

MEHTA, ASHWIN D

ART UNIT	PAPER NUMBER
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1638

DATE MAILED: 06/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/309,038

Applicant(s)

HEIFETZ ET AL.

Examiner

Ashwin Mehta

Art Unit

1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 April 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-12,14-40,46-50,52,56-58,60-63,65,69 and 73-75 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-12,14-40,46-50,52,56-58,60-63,65,69 and 73-75 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. The objections to claims 2, 13 and 64 are moot, in light of their cancellation.
3. The rejection to claim 70 under 35 U.S.C. 112, 2nd paragraph, is moot, in light of its cancellation.

Claim Rejections - 35 USC § 112

4. Claims 56-58, 60, and 61 remain and claims 15, 16, and 73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons of record stated in the Office action mailed 11 October 2001 under item 8. Applicants traverse the rejection in the paper received 08 April 2002. Applicants' arguments have been fully considered but were not found persuasive. Applicants argue that claim 56 was amended to be dependent on claim 61, which is dependent on claim 59 (response, page 2, second to last full paragraph). However, claim 56 has not been amended, and claim 59 has been cancelled (response, page 2, first line). Claim 73 is also dependent on cancelled claim 59.

In claims 15 and 16: the claims are dependent on cancelled claim 13.

5. Claims 1, 3-12, 14-40, 46-48, 49 (amended) 50, 52, 56-58, 60-63, 65, 69 (amended), and 73-75 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record stated in the Office action mailed 11 October 2001 under item 9. Applicants traverse the rejection in the paper received 08 April 2002. Applicants' arguments were fully considered but were not found persuasive.

Applicants argue that the present invention describes the use of dsRNA molecules for a target gene of interest, specifically a virus or portion thereof, that the crux is that the nucleotide sequence and function thereof can be of any gene of interest or virus or portion thereof, and that the important aspect is that the RNA molecule(s) form a dsRNA structure (response, page 3, 3rd full paragraph). Applicants argue that the specification at pages 17-19 describes that dsRNA is used to control any number of viruses, and that preferred sequences are either from protein coding regions or portions thereof, or non-translated sequences (response, page 3, 4th full paragraph). However, the use of a nucleotide sequence does not describe the nucleotide sequence itself. One cannot use the RNA molecule(s) without a description of the sequences of either the sense or antisense strand of the dsRNA molecule. The specification does not describe the sequences of all of the RNA molecules encompassed by the broad scope of the claims. Applicants are also not in possession of constructs that comprise DNA or RNA sequences of viral genomes that are yet to be discovered.

6. Claims 1, 3-12, 14-40, 46-48, 49 (amended) 50, 52, 56-58, 60-63, 65, 69 (amended), and 73-75 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record stated in the Office action mailed 11 October 2001 under item 10. Applicants traverse the rejection in the paper received 08 April 2002. Applicants' arguments were fully considered but were not found persuasive.

Applicants argue that the specification does not have to describe every possible embodiment covered by the claims (response, page 4, 3rd full paragraph). However, the claims encompass nucleotide sequences of all viral genomes, including those that have yet to be discovered. One skilled in the art cannot be enabled to practice the invention with undiscovered viral genomes. See In re Bell, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and In re Deuel, 34 USPQ2d, 1210 (Fed. Cir. 1995), which teach that the mere existence of a protein does not enable claims drawn to a nucleic acid encoding that protein. See also Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 at 1021 and 1027, (Fed. Cir. 1991) at page 1021, where it is taught that a gene is not reduced to practice until the inventor can define it by "its physical or chemical properties" (e.g. a DNA sequence). The specification also does not provide any guidance regarding the portion of the viral genomes that would be effective with the claimed invention. A single base pair is encompassed by a "portion," yet clearly this is not sufficient to confer virus resistance or tolerance to a cell.

Applicants argue, regarding the issue that the invention would not reduce expression of viral genomes that have PTGS suppressors, that Vionnet et al. only show

that the pattern of PTGS (post-transcriptional gene silencing) is tissue or leaf-age specific, and that the reference fails to teach that viruses that encode a suppressor fail to alter the resistance or susceptibility of the plant to viral infection (response, page 5, 2nd full paragraph). Vionnet et al. assert that some viruses induce an RNA-mediated defense response, which is similar to PTGS, in non-transgenic plants. Vionnet et al. also assert that the ability of viruses to infect plants indicates that they have evolved to avoid or suppress this RNA-mediated defense. Vionnet et al. review previous studies, which taught that these viruses encode suppressors of PTGS, and that the suppression acts against the RNA-mediated defense. Vionnet et al. conclude that the outcome of their experiments was consistent with the previous results that indicated that suppression of gene silencing is a widespread strategy among plant viruses (page 14147). Applicants' invention follows or "takes advantage of" the RNA-mediated defense response of plants to confer resistance to viruses. However, as Vionnet et al. assert, it is known that many viruses encode suppressors of this defense mechanism, and it is not clear how one skilled in the art can use the claimed invention to confer resistance or tolerance to cells against such viruses.

Applicants also cite numerous references demonstrating the use of RNA interference in mammalian cells, and argue that although these articles were published after the filing date of the instant application, they represent evidence of the operability of the teachings of the application (response, page 5, 3rd full paragraph to page 6, 1st full paragraph). However, only one of these teachings concerns virus resistance, and it is a meeting abstract (John et al.). As the full teachings represented by this abstract were not provided, a full review of this reference cannot be made. Further, the references do not

address the enablement of the claimed invention in all cell types. Oates et al. (Dev. Biol., 2000, Vol. 224, pages 20-28) for example, investigate the ability of dsRNA to inhibit gene expression in zebrafish, but found that numerous unrelated genes, in addition to the intended target gene, were also affected (abstract, pages 22-25). Applicants' arguments do not address the enablement of the claimed invention with all cell types.

Regarding claims 56-58 and the issue of inheritance by progeny of RNA molecules, Applicants argue that the claims are ultimately dependent on claim 12 which is directed to methods comprising introducing DNA into cells (response, page 6, 2nd full paragraph). However, claim 56 has not been amended. It is also noted that Applicants have not addressed an issue that further regards claims 31-33 (page 6 of the last Office action), which concerns the expression of sense and antisense RNA sequences in the same transcript, when the corresponding DNA sequences are separated on the DNA molecule by a functional gene, which presumably comprises a transcription termination sequence.

Claim Rejections - 35 USC § 103

7. Claims 1, 3-12, 14-30, 33-40, 46-48, 49 (amended) 50, 52, 56-58, 60-63, 65, 69 (amended), and 73-75 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sijen et al. in view of Fire et al., Applicants' admitted state of the prior art, and Keddie et al., for the reasons of record stated in the Office action mailed 11 October 2002 under item 12. Applicants traverse the rejection in the paper received 08 April 2002.

Applicants' arguments have been fully considered but were not found persuasive. Applicants argue that Fire et al. merely propose that RNA interference might also operate

in plants, but provide no reasonable expectation of success and that Sijen et al. do not, either (response, page 3rd full paragraph). However, the demonstration of the dsRNA strategy by Fire et al. and the suggestion of Sijen et al. that formation of dsRNA molecules is part of the silencing process does provide a reasonable expectation of success.

Summary

8. No claim is allowed.
9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Contact Information

Any inquiry concerning this or earlier communications from the examiner should be directed to Ashwin Mehta, whose telephone number is 703-306-4540. The examiner can normally be reached on Mondays-Thursdays and alternate Fridays from 8:00 A.M to 5:30 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 703-306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 and 703-872-9306 for regular communications and 703-872-9307 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

A handwritten signature in black ink, appearing to read "Amy Nelson", with a stylized flourish at the end.

A.M.
June 24, 2002

**AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
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